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Transformation of Tazettine to Pretazettine[1]

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Pretazettine (**1**), which shows antileukemic activity, was obtained by conversion of tazettine (**2**) to 3-epitazettadiol (**3**) [whose structure was confirmed by its cyclization to deoxypretazettine (**4**)], followed by manganese dioxide oxidation of **3**. The transformation of **2** to **1** confirmed the stereochemistry of pretazettine (**1**).

Keywords——pretazettine; tazettine; 3-epitazettadiol; deoxypretazettine; deoxypretazettine neomethine; antileukemic activity; stereochemistry; manganese dioxide; Amaryllidaceae; NMR

We have previously reported[3,4] the isolation of pretazettine (**1**),[5] which shows antileukemic activity,[6] from the bulbs of *Zephyranthes carinate* HERB. and *Lycoris radiata* HERB. (Amaryllidaceae).

This paper describes the transformation of tazettine (**2**),[7] which was found[5] to be an extraction artifact of **1**, to pretazettine (**1**), *via* 3-epitazettadiol (**3**), whose stereochemistry was confirmed both by its cyclization to deoxypretazettine (**4**) and by conversion of **4** to deoxypretazettine neomethine (**5**).

Reduction of tazettine (**2**) with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) gave two crystalline isomers, tazettadiol (**6**)[8–10] (62.7%) and a new minor product (13.5%), 3-epitazettadiol (**3**), $C_{18}H_{23}NO_5$, mp 139—141°, $[\alpha]_D^{20}$ +95.0° (c=1.0, ethanol). The structure of **3** was deduced from spectral data. The infrared (IR) spectrum showed absorptions due to a hydroxyl group at 3440 cm^{-1} and a double bond at 1620 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum given in Table I was very similar to that of **6** and the assignment of the following signals was achieved by a nuclear magnetic double resonance (NMDR) experiment. First, monitoring the line (δ 6.67) of C-6′-H gave an NOE (intramolecular nuclear Overhauser effect) peak at δ 2.71, since irradiation at δ 2.71 (C-7a-H) gave a 17% NOE increment in the signal of C-6′-H. This irradiation at δ 2.71 reduced a multiplet at δ 5.73 (C-4-H)

1) Part of this work was published as a communication: S. Kobayashi, M. Kihara, and T. Shingu, *Heterocycles*, **12**, 1547 (1979).
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3) S. Kobayashi, H. Ishikawa, M. Kihara, T. Shingu, and T. Hashimoto, *Chem. Pharm. Bull.*, **25**, 2244 (1977).
4) S. Kobayashi, S. Takeda, H. Ishikawa, H. Matsumoto, M. Kihara, T. Shingu, A. Numata, and S. Uyeo, *Chem. Pharm. Bull.*, **24**, 1537 (1976).
5) *a)* W.C. Wildman and D.T. Bailey, *J. Am. Chem. Soc.*, **89**, 5514 (1967); *b) Idem, ibid.*, **91**, 150 (1969); *c) Idem, J. Org. Chem.*, **33**, 3749 (1968).
6) *a)* E. Furusawa, N. Suzuki, S. Tani, S. Furusawa, G.Y. Ishioka, and J. Motobu, *Proc. Soc. Exp. Biol. Med.*, **143**, 33 (1973); *b)* E. Furusawa, N. Suzuki, S. Furusawa, and J.Y.B. Lee, *ibid.*, **149**, 771 (1975); *c)* E. Furusawa, S. Furusawa, S. Tani, H. Irie, K. Kitamura, and W.C. Wildman, *Chem. Pharm. Bull.*, **24**, 336 (1976).
7) This alkaloid has been reviewed by J.W. Cooks and J.D. London, and W.C. Wildman in R.H.F. Manske "The Alakaloids," Vol. II (1952), VI (1960), and XI (1968), Academic Press, Inc., New York.
8) T. Ikeda, W.I. Yaylor, Y. Tsuda, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, **1956**, 4749.
9) S. Kobayashi, M. Kihara, T. Hashimoto, and T. Shingu, *Chem. Pharm. Bull.*, **24**, 716 (1976).
10) T. Kitagawa, S. Uyeo, and N. Yokoyama, *J. Chem. Soc.*, **1959**, 3741.

to a double doublet (the long-range coupling disappeared). Irradiation at δ 4.84 (C-7′-H) gave a 20% NOE increment in the signal (δ 6.96) of C-3′-H. Irradiation at δ 4.36 (C-3-H) reduced a double doublet at δ 2.37 of C-2-Hβ to a doublet.

The following mechanism has been suggested to account for formation of both **3** and **6** on hydride reduction of **2** (see Chart 2): addition of the AlH_4^- nucleophile (with the stereo-

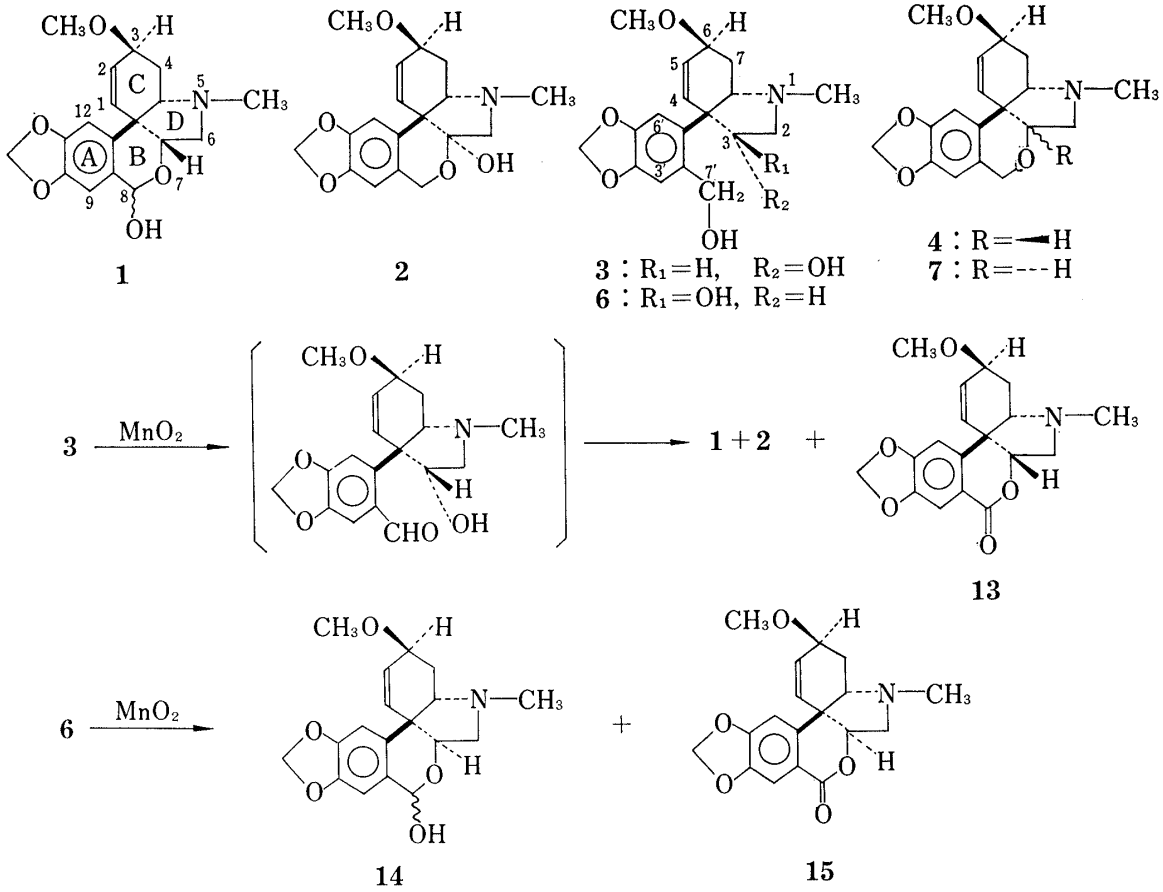

Chart 1

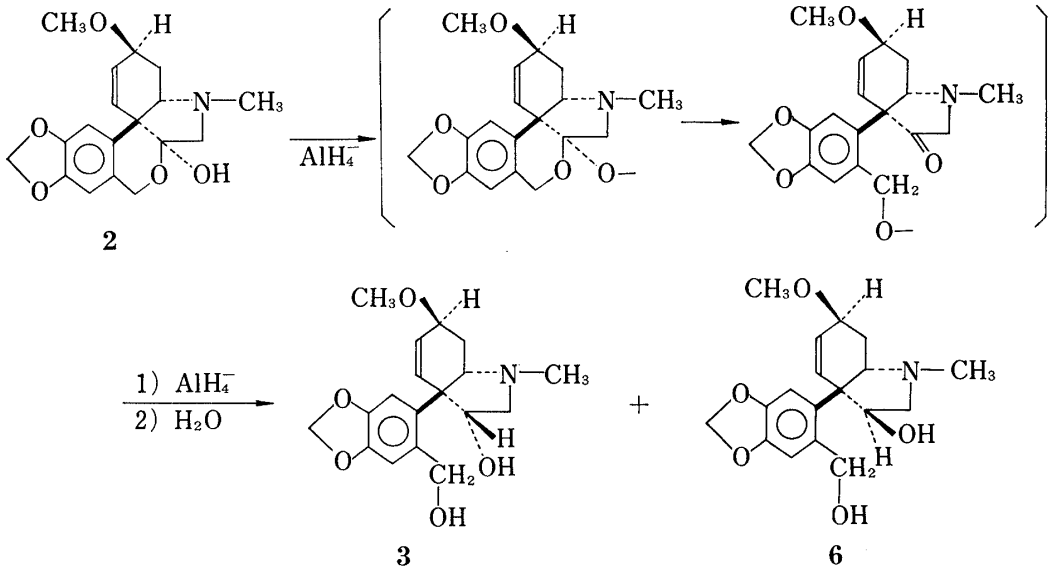

Chart 2

Table I. NMR Data for 3-Epipretazettadiol (**3**) and Tazettadiol (**6**) ($CDCl_3$, δ)[a]

Compd.	C-6′-H	C-3′-H	C-4-H	C-5-H	OCH_2O	C-7′H_2	C-6-H	C-3-H
3	6.67	6.96	5.73 (m, $J_{4-5}=11$, $J_{4-6}=2$, $J_{4-7a}=2$)	5.94 (m, $J_{5-4}=11$)	5.90	4.84 (d, $J=12$) 4.72 (d, $J=12$)	3.93 (m, $J_{6-7\beta}=10$, $J_{6-7\alpha}=5$)	4.36 (dd, $J_{3-2\beta}=6$, $J_{3-2\alpha}=1$)
6[b]	6.79	6.87	5.80 (br s)	5.80 (br s)	5.92	4.78 (d, $J=12$) 4.54 (d, $J=12$)	3.89 (m, $J_{6-7\beta}=10$, $J_{6-7\alpha}=6$)	4.36 (dd, $J_{3-2\alpha}=6$, $J_{3-2\beta}=5$)

Compd.	C-2		OCH_3	NCH_3	C-7a-H	C-7	
	Hα	Hβ				Hα	Hβ
3	2.96 (dd, $J_{2\alpha-2\beta}=10$, $J_{2\alpha-3}=1$)	2.37 (dd, $J_{2\beta-2\alpha}=10$, $J_{2\beta-3}=6$)	3.37	2.31	2.71 (m)	*c*)	1.72 (m, $J_{7\beta-7\alpha}=14$, $J_{7\beta-6}=10$, $J_{7\beta-7a}=2$)
6[b]	3.62 (dd, $J_{2\alpha-2\beta}=11$, $J_{2\alpha-3}=6$)	2.23 (dd, $J_{2\beta-2\alpha}=11$, $J_{2\beta-3}=5$)	3.33	2.42	3.08 (m)	2.41 (m, $J_{7\alpha-7\beta}=13$, $J_{7\alpha-6}=6$, $J_{7\alpha-7a}=2$)	1.78 (m, $J_{7\beta-7\alpha}=13$, $J_{7\beta-6}=10$)

a) All signals are singlets except where otherwise indicated in parentheses.
b) See Ref. 9.
c) Obscured signal.

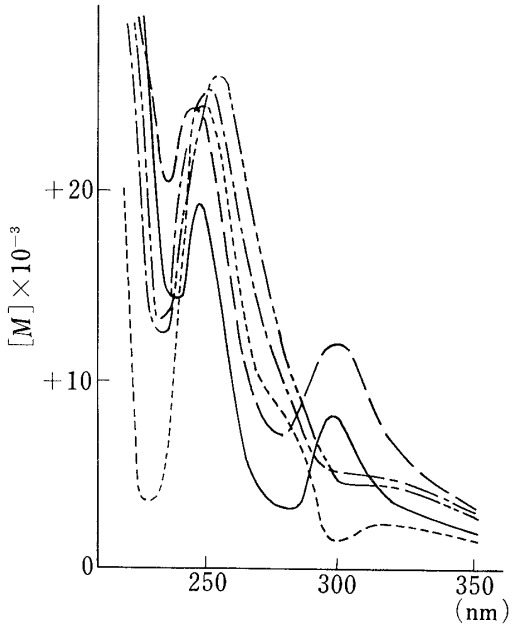

Fig. 1. ORD Spectra of **1**, **2**, **4**, **7**, and **14** in MeOH

1: ———, **2**: ----------, **4**: – – – –, **7**: – – – – –, **14**: – – – – – –.

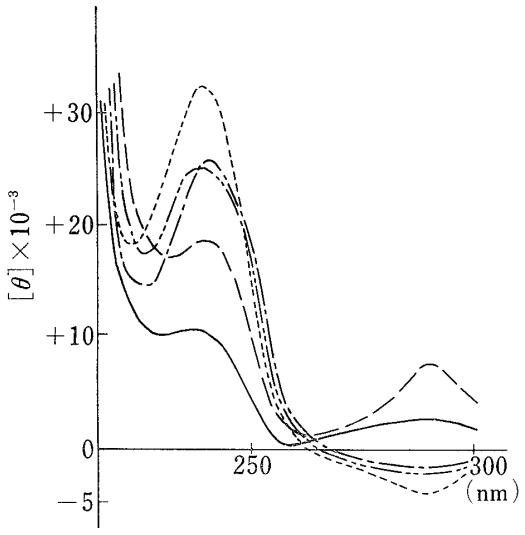

Fig. 2. CD Spectra of **1**, **2**, **4**, **7**, and **14** in MeOH

1: ———, **2**: ----------, **4**: – – – –, **7**: – – – – –, **14**: – – – – – –.

TABLE II. NMR Data for Pretazettine and Related Compounds ($CDCl_3$, δ)[a]

Compd.	C-12-H	C-9-H	C-2-H[b]	C-1-H[c]	OCH_2O	C-8 H_2 (or H)	C-3-H	C-6a-H[d]
1	6.74	6.83	5.86 (m)	5.50 (m, 11, 2, 2)	5.89	6.07	4.16 (m)	4.32 (dd)
2[h]	6.84	6.48	6.12 (m)	5.61 (m)	5.88	4.97(d) 4.62(d)	4.06 (m)	
4	6.77	6.48	5.87 (m)	5.63 (m, 11, 2, 2)	5.89	4.99	4.14 (m)	3.86 (dd)
7[h]	6.91	6.50	6.02 (m, 10, 2, 2)	5.38 (m, 10, 2, 2)	5.88	4.59 (br s)	4.03 (m)	4.00 (dd)
13	6.74	7.50	5.97 (m)	5.46 (m, 11, 2, 2)	6.03		4.16 (m)	4.47 (dd)
14	6.88	6.73	6.07 (m)	5.34 (m, 11, 2, 2)	5.89	5.83[i] 5.76	4.16 (m)	4.40 (dd)
15	6.87	7.54	6.21 (m, 11, 2, 1)	5.36 (m, 11, 2, 2)	6.02		4.14 (m)	4.69 (dd)

compd.	C-6		OCH_3	NCH_3	C-4a-H	C-4	
	$H\alpha$[e]	$H\beta$[f]				$H\alpha$	$H\beta$[g]
1	2.97 (dd, 11, 10)	2.63 (dd, 8, 10)	3.41	2.48	2.93	2.47 (m)	1.71 (m, 14, 10, 2)
2[h]	3.29 (d, 10)	2.67 (d, 10)	3.45	2.40	2.86 (m)	2.22 (m)	1.61 (m, 13, 10, 2)
4	2.94 (dd, 11, 10)	2.62 (dd, 8, 10)	3.41	2.48	2.92 (m)	*j*)	1.77 (m, 14, 9, 2)
7[h]	3.43 (dd, 5, 11)	2.51 (dd, 3, 11)	3.43	2.39	2.64 (m)	2.24 (m)	1.70 (m, 13, 10, 3)
13	3.18 (dd, 11, 10)	2.79 (dd, 8, 10)	3.41	2.52	3.12 (m)	*j*)	1.70 (m, 13, 10, 2)
14	3.49 (dd, 5, 12)	2.56 (dd, 1, 12)	3.44	2.47	2.84 (m)	*j*)	1.68 (m, 14, 10, 3)
15	3.52 (dd, 4, 12)	2.86 (dd, 1, 12)	3.44	2.50	2.98 (m)	2.24 (m)	1.51 (m, 14, 10, 2)

a) All signals are singlets unless otherwise indicated in parentheses.
b) The numerical values in parentheses are J_{2-1}, J_{2-3}, and J_{2-4}, respectively, as Hz value.
c) The numerical values in parentheses are J_{1-2}, J_{1-3}, and J_{1-4a}, respectively.
d) The coupling constants are given in Table III.
e) The numerical values in parentheses are $J_{6\alpha-6a}$ and $J_{6\alpha-6\beta}$, respectively.
f) The numerical values in parentheses are $J_{6\beta-6a}$ and $J_{6\beta-6\alpha}$, respectively.
g) The numerical values in parentheses are $J_{4\beta-4\alpha}$, $J_{4\beta-3}$, and $J_{4\beta-4a}$, respectively.
h) See Ref. 9.
i) See Ref. 5*b*.
j) Obscured signals.

Table III. Coupling Constant $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in **1**, **4**, **7**, and **13**—**15** (Hz)

	1	**4**	**13**	**7**	**14**	**15**
$J_{6a-6\alpha}$	11	11	11	5	5	4
$J_{6a-6\beta}$	8	8	8	3	1	1

chemical restraints of the β-bonded phenyl group) to a carbonyl function in a keto-alkoxide intermediate derived from an alkoxide of **2**, gives **6** as a major product, while addition from the hindered side gives **3** as a minor product. This configuration of C-3 in **3** and **6** was also established by a cyclization reaction of these compounds.

A cyclization product, deoxypretazettine (**4**) (44.4%), $C_{18}H_{21}NO_4$, mp 112—113°, was obtained when the diol (**3**) was treated with 3% sulfuric acid in the same way as for deoxytazettine (**7**).[8,9] The chemical shifts of **4** are given in Table II. The stereochemistry of **4** was clearly characterized by the following spectroscopic features: both its optical rotatory dispersion (ORD) and circular dichroism (CD) spectra, having positive Cotton effects centered at 290 nm, are similar to those of **1**, but different from those of **2** and **7**, which have negative Cotton effects (see Figs. 1 and 2). Furthermore, as shown in Table III, the coupling constants $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in **4** are larger than those in **7**. These findings indicate that **4**, as well as **1**, has a B/D *trans* configuration and is an epimer of **7** at C-6a, while **7** has the same configuration as **2** and a B/D *cis* configuration. On the basis of these conclusions, the diols **3** and **6** can be assigned the *R*- and *S*-configuration, respectively, at C-3, since no epimerization was observed during cyclization of **3** to **4**: nucleophilic attack of the secondary hydroxyl function in **3** or **6** on the benzyl cation derived from **3** or **6** by protonation at its benzyl hydroxyl group gave the cyclization product **4** or **7**.

The above conclusion regarding the stereochemistry of **4** was also supported by conversion of **4** to deoxypretazettine neomethine (**5**)[an enantiomer of deoxytazettine neomethine (**8**)],[8,9,11] *via* deoxypretazettine methine (**9**) [an enantiomer of deoxytazettine methine (**10**)].[8,9] The

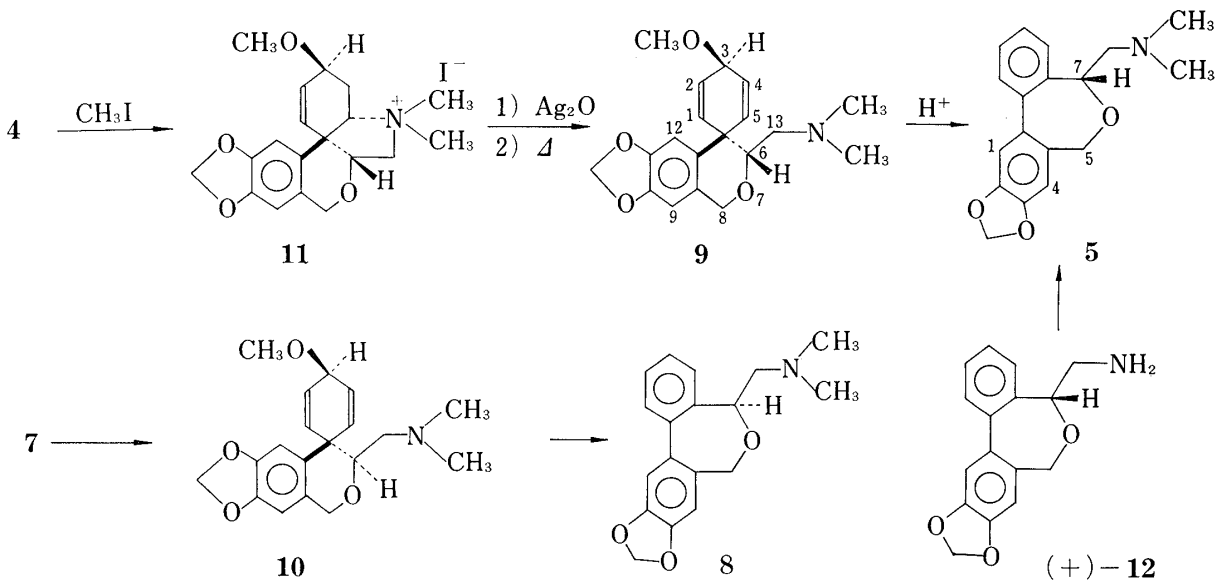

Chart 3

11) Warnhoff reported that the configuration at C-6a in **7** would be unaffected during the degradation of **7** to **8** and especially during the conversion of **10** to **8** [E.W. Warnhoff, "Molecular Rearrangement," Vol. 2, P.de Mayo, Ed., Interscience Publishers, Inc., New York. N.Y., 1964, p. 851].

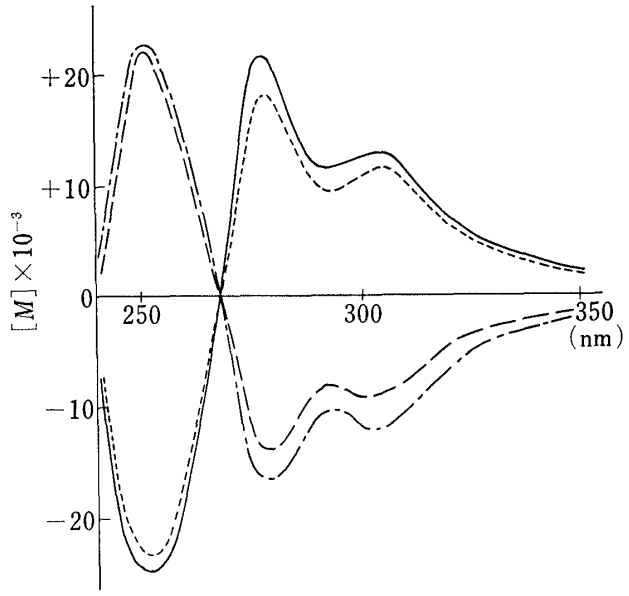

Fig. 3. ORD Spectra of **5** and **8** in MeOH
5 from **9**: ———, **5** from (+)-**12**: ----------,
8 from **10**: – – – –, **8** from (−)-**12**: –·–·–·–.

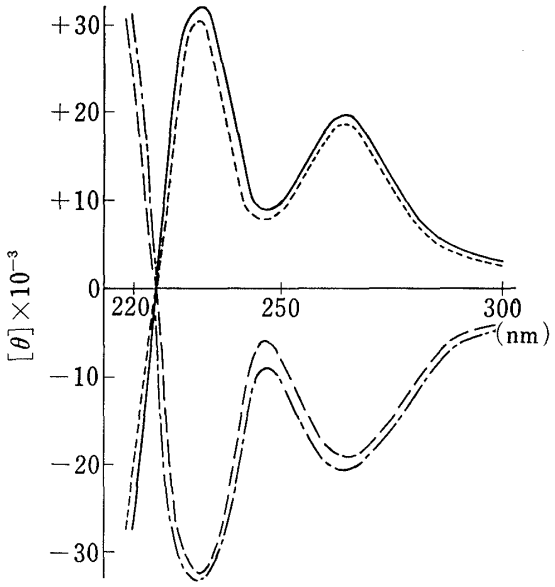

Fig. 4. CD Spectra of **5** and **8** in MeOH
5 from **9**: ———, **5** from (+)-**12**: ----------,
8 from **10**: – – – –, **8** from (−)-**12**: –·–·–·–.

methine (**9**), prepared by Hofmann degradation of the methiodide (**11**) of **4**, showed $[\alpha]_D^{28}$ +65.7° (c=1.41, ethanol), while **10** showed $[\alpha]_D^{17}$ −64.2° (ethanol).[8] The NMR spectrum of **9** was found to be identical with that of **10**. Rearrangement of **9** with hydrochloric acid gave an amorphous neomethine (**5**), $C_{18}H_{19}NO_3$, $[\alpha]_D^{29}$ +39.1° (c=0.64, ethanol). This neomethine was characterized by means of its NMR spectrum (see "Experimental"), which is identical with that of **8**.

On the other hand, the structure of this compound from the natural source was confirmed by synthesis of **5** from (+)-7-aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin [(+)-**12**], which was obtained by resolution of the corresponding racemic compound [(±)-**12**][9] with di-*p*-toluoyl-L-tartaric acid. Eschweiler-Clarke methylation of (+)-**12** gave 7-dimethylaminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin, $[\alpha]_D^{21}$ +37.1° (c=0.7, ethanol), which was found to be identical with the neomethine (**5**) obtained from **4** by comparison of their NMR, ORD, and CD spectra (see Figs. 3 and 4). The specific rotations, ORD, and CD spectra of **5** and **8** are equal in magnitude though opposite in sign or direction, as shown in Figs. 3 and 4. Therefore, the neomethine (**5**) is an optical antipode of **8** and has the *R*-configuration at C-7, since the *R*-configuration at C-6a in **4** would be unaffected during the degradation of **4** to **9**.[11] This conclusion also supports the finding that **3** has the R-configuration at C-3. On the basis of these results, we attempted to convert the diol **3** to pretazettine (**1**).

Oxidation of **3** in chloroform with manganese dioxide at room temperature gave three products, pretazettine (**1**)[3-5] (amorphous) (29.5%), 3-epimacronine (**13**)[5c] (21.6%), mp 125—127°, and tazettine (**2**)[7] (9.4%), mp 202—203°. These products were characterized by means of their NMR spectra, as listed in Table II. The base **1** was crystallized as its hydrochloride, mp 223—224° (dec.), $C_{18}H_{21}NO_5 \cdot HCl$, and picrate, mp 202—203°, which were identical with those of authentic samples of **1** by direct comparison. The base **13** is a further oxidation product of **1**, while **2** appears to be an extraction artifact of **1**.

Similar oxidation of the diol **6** gave 6a-epipretazettine (**14**)[5b] (amorphous) (35.2%) and a new product 6a-epi-3-epimacronine (**15**) (20.4%), mp 105—108°, $C_{18}H_{19}NO_5$. The structures of the two products were determined by NMR spectroscopy (see Table II). On the basis of the coupling constants $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ in these oxidation products, it is concluded that **1** and **13** have the same R-configuration at C-6a as that of **3** at C-3, while **14** and **15** have the S-con-

figuration at C-6a (see Table III).

NMR Spectra of Pretazettine (1) and Related Compounds

R-Type compounds (such as **1** and **4**) having the *R*-configuration at C-6a, were distinguished from S-type compounds (such as **7** and **14**) having the S-configuration at C-6a, by NMR spectroscopic evidence. First, a clear difference in the coupling constants of $J_{6a-6\alpha}$ and $J_{6a-6\beta}$ between these two types of compound was observed, as mentioned above. Secondly, the signals (δ 2.94—2.97) of C-6-Hα in the *R*-type compounds (**1** and **4**) appeared at higher field than those (δ 3.43—3.49) of the *S*-type compounds (**14** and **7**), indicating that α-protons at C-6 in the former are more shielded by the double bond at C-1 than those in the latter. For the same reason, the diols **3** and **6** were concluded to be *R*- and *S*-type compounds, respectively, since the signal of C-2-Hα (which corresponds to C-6-Hα in four-ring-system compounds) of **3** and **6** appeared at δ 2.96 and 3.62, respectively. Thirdly, irradiation of the signals of C-6a-H in the *S*-type compounds (**7**, **14**, and **15**) gave NOE increments (7, 8, and 5%, respectively) in the signals of C-1-H, but this was not the case in the *R*-type compounds. In contrast, since the spatial relation of C-1-H to the 7-oxygen is 1,3-diaxial-like in the *R*-type compounds, the signals of C-1-H in **1** and **4** appeared at lower field than those of the *S*-type compounds (**14** and **7**, respectively) (see Table II). The chemical shifts of C-2-H and C-12-H in the *R*-type compounds (**1**, **4**, and **13**) appeared at higher field than the corresponding signals of the *S*-type compounds (**14**, **7**, and **15**, respectively).

Irradiation of the signals of C-4-Hβ in **4** and **13** (*R*-type compounds) and in **7** and **15** (S-type compounds) gave NOE increments (10, 10, 11, and 8%, respectively) in the signals of C-12-H. This indicates that the spatial relation of ring A to ring C is very similar in the two types of compounds, and that ring C in these compounds has a half-chair conformation, as in **1** and **2**.

Experimental

All melting points are given as uncorrected values. The spectrophotometers used were a Hitachi model EPI-G2 for IR spectra, a Shimadzu model UV-200 for UV spectra, a Yanagimoto model OR-50 for optical rotations, a JASCO model ORD/UV-5 for ORD spectra, a JASCO model J-40C for CD spcctra, and a JEOL model JNM-PS-100 or a Hitachi model R-22 for NMR spectra, using TMS as an internal standard. The plates used for preparative thin-layer chromatography (PLC) were coated with aluminum oxide (Merck, GF_{254}) and silica gel (Kieselgel, PF_{254} Merck).

Lithium Aluminum Hydride Reduction of Tazettine (2)——A mixture of **2** (1.985 g), dry THF (65 ml), and LAH (750 mg) was stirred at room temperature for 10 hr. After addition of $CHCl_3$ (30 ml) and H_2O (3 ml), the mixture was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated to give an oil (2.2 g), which was triturated with acetone to afford **6** (1.137 g) as white needles, mp 114—118° (lit.[9] mp 117—119°). This compound was identical with a sample of **6**[9] by direct comparison. The mother liquor separated from **6** was subjected to PLC using Al_2O_3–[benzene–acetone (4:1)]. Elution of materials of *Rf* 0.05—0.19 with $CHCl_3$–MeOH–acetone (1:1:1) gave an oil (391 mg), which was triturated with acetone–ether to afford **3** (270 mg, 13.5%) as white prisms, mp 139—141°. *Anal.* Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.81; H, 6.98; N, 4.20. UV λ_{max}^{MeOH} nm (log ε): 288 (3.55), 242 (3.77). Elution of materials of *Rf* 0.35—0.57 with the same solvents gave additional **6** (116 mg, total 1.253 g, 62.7%).

Deoxypretazettine (4)——A solution of **3** (19 mg) in 3% H_2SO_4 (3 ml) was heated at 100° for 1.5 hr. The reaction mixture was washed with ether, made basic with Na_2CO_3, dried, and concentrated *in vacuo* to give an oil (16 mg). The oil was subjected to PLC using Al_2O_3–[benzene–acetone (4:1)]. Elution of materials of *Rf* 0.69—0.83 with $CHCl_3$–MeOH–acetone (1:1:1) gave **4** (8 mg, 44.4%), mp 112—113° (from ether). $[\alpha]_D^{21}$ +307.0° (c=0.6, EtOH). *Anal.* Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.76; H, 6.75; N, 4.41. IR ν_{max}^{KBr} cm^{-1}: 1620 (C=C). UV λ_{max}^{MeOH} nm (log ε): 290 (3.63), 241 (3.74). ORD (c=0.0105, MeOH) [M]^{20} (nm): +12000° (298) (peak), +7180° (279) (trough), +24600° (242) (peak), +20400° (236) (trough), +29400° (225). CD (c=0.0097, MeOH) [θ]^{23} (nm): +4550 (300), +7790 (290), +974 (263), +18810 (238), +16860 (231), +34650 (220).

Deoxypretazettine Methiodide (11)——A solution of **4** (27 mg) and methyl iodide (1 g) in MeOH (2 ml) was refluxed for 3 hr. Work-up in the usual way gave **11** (30 mg, 76.9%) as white needles, mp 237—238° (dec.) (from acetone). *Anal.* Calcd for $C_{19}H_{24}INO_4$: C, 49.90; H, 5.29; N, 3.06. Found: C, 49.50; H, 5.18; N, 2.91.

Deoxypretazettine Methine (9)——A mixture of **11** (35 mg) in H_2O (3 ml) and Ag_2O (from 85 mg of $AgNO_3$ and excess 5% NaOH) was stirred at room temperature for 1 hr. The filtrate was evaporated to dryness

under reduced pressure and the residue was heated in a vacuum at 100° for 30 min. Work-up in the usual way gave **9** (22 mg, 88.0%) as an oil. NMR ($CDCl_3$) δ: 6.69 (1H, s, C-12-H), 6.44 (1H, s, C-9-H), 6.16—5.68 (4H, m, C-1, 2, 4, and 5-H), 5.87 (2H, s, OCH_2O), 4.81 (2H, s, C-8H_2), 4.38 (1H, br s, C-3-H), 3.65 (1H, dd, $J_{6-13l}=8$, $J_{6-13h}=2$ Hz, C-6-H), 3.44 (3H, s, OCH_3), 2.42 [1H, dd, $J_{13l-13h}=13$, $J_{13l-6}=8$ Hz, C-13-H (lower)], 2.28 [6H, s, $N(CH_3)_2$], 2.20 (1H, dd, $J_{13h-13l}=13$, $J_{13h-6}=2$ Hz, C-13-H (higher)]. These NMR spectral data are consistent with those of deoxytazettine methine (**10**).[9]

Resolution of (±)-7-Aminomethyl-5,7-dihydro-2,3-methylenedioxydibenz[*c*,*e*]oxepin [(±)-12] with Di-p-toluoyl-L-tartaric Acid——A solution of (±)-**12** (162 mg) and di-*p*-toluoyl-L-tartaric acid (257 mg) in MeOH (1 ml) was left to stand at room temperature overnight to give the tartrate (58 mg) as white needles, mp 194—195° (dec.) (from MeOH). This salt was dissolved in H_2O (10 ml), made basic with 10% NaOH, and extracted with $CHCl_3$. Work-up in the usual way gave an oil (28 mg), which was triturated with ether to afford (+)-**12**, mp 121—123° (from ether). $[\alpha]_D^{20}$ +39.0° (c=1.0, EtOH). NMR ($CDCl_3$) δ: 6.99 (1H, s, C-1-H), 6.86 (1H, s, C-4-H), 5.99 (2H, s, OCH_2O), 4.40 and 4.08 (each 1H, d, J=12 Hz, AB-type of C-5H_2), 4.22 (1H, m, C-7-H), 3.06 (2H, m, C-13H_2), 2.02 (2H, br s, NH_2). This spectrum was identical with that of (−)-**12**.[9]

Deoxypretazettine Neomethine (5)——(i) From **9**: A solution of **9** (21 mg) in 5% HCl (3 ml) was stirred at room temperature for 1 hr. The reaction mixture was extracted with ether, dried, and concentrated to give 6-phenylpiperonylalcohol (3 mg), mp 97—98°, (lit.[8] mp 102—104°). *Anal.* Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.65; H, 5.22. NMR ($CDCl_3$) δ: 7.36 (5H, m, aromatic H), 7.03 (1H, s, C-2-H or C-5-H), 6.76 (1H, s, C-5-H or C-2-H), 5.99 (2H, s, OCH_2O), 4.49 (2H, s, ArC$\underline{H}_2$OH). The acidic aqueous solution separated from the ethereal extract was made basic with Na_2CO_3 and extracted with ether. The extract gave **5** (10 mg, 52.6%) as an oil. NMR ($CDCl_3$) δ: 7.42 (4H, s, aromatic H), 7.00 (1H, s, C-1-H), 6.87 (1H, s, C-4-H), 6.00 (2H, s, OCH_2O), 4.38 (1H, dd, $J_{7-12h}=5$, $J_{7-12l}=8$ Hz, C-7-H), 4.36 and 4.04 (each 1H, d, J=12 Hz, AB-type of C-5H_2), 2.92 [1H, dd, $J_{12l-12h}=12$, $J_{12l-7}=8$ Hz, C-12-H (lower)], 2.58 [1H, dd, $J_{12l-12h}=12$, $J_{12h-7}=5$ Hz, C-12-H (higher)], 2.23 [6H, s, $N(CH_3)_2$]. This NMR spectrum was identical with that of **8**.[9] ORD (c=0.0045, MeOH) [M]^{27} (nm): +3300° (350), +11900° (306) (peak), +11200° (290) (trough), +22400° (278) (peak), 0° (268), −22400° (253) (trough), −1980° (240). CD (c=0.0102, MeOH) [θ]^{25} (nm): +4390 (290), +19870 (265), +8750 (246), +32670 (232), 0 (222), −39140 (215).

The oil (**5**) was crystallized as its hydrochloride, mp 218—219° (from acetone). *Anal.* Calcd for $C_{18}H_{19}NO_3\cdot HCl\cdot 1/2H_2O$: C, 63.06; H, 6.18; N, 4.09. Found: C, 62.86; H, 6.33; N, 3.97.

(ii) From (+)-**12**: A mixture of (+)-**12** (21 mg), HCOOH (0.5 ml) and formalin (0.3 ml) was heated in a sealed tube at 100° for 14.5 hr. Work-up in the usual way gave **5** (14 mg, 60.5%) as an oil. $[\alpha]_D^{21}$ +37.1° (c=0.7, EtOH). ORD (c=0.0023, MeOH) [M]^{20} (nm): +4510° (350), +12860° (306) (peak), +9650° (292) (trough), +17880° (278) (peak), 0° (268), −23140° (252) (trough), −7720° (242). CD (c=0.0086, MeOH) [θ]^{20} (nm): +4820 (290), +19370 (265), +7590 (246), +30390 (232), 0 (222), −33830 (215). The oil (**5**) was converted to its hydrochloride, mp 221—222°. The free neomethine and its hydrochloride obtained by method (i) were identical with those prepared from (+)-**12** by method (ii) as judged by direct comparison.

Oxidation of 3-Epitazettadiol (3) with MnO_2——A mixture of **3** (75 mg) in $CHCl_3$ (7 ml) and MnO_2[12] (375 mg) was stirred at room temperature for 80 min. Work-up in the usual way gave an oil (81 mg), which was subjected to PLC using SiO_2-[$CHCl_3$-MeOH-diethylamine (92: 3: 5) to afford three fractions: I, *Rf* 0.36—0.48; II, *Rf* 0.56—0.61; III, *Rf* 0.72—0.81. Each fraction was eluted with $CHCl_3$–MeOH–acetone (1: 1: 1). Fraction I gave **1** (22 mg, 29.5%). UV λ_{max}^{MeOH} nm (log. ε): 291 (3.64), 241 (3.67). ORD (c=0.0092, MeOH) [M]^{27} (nm): +4700° (310), +7940° (294) (peak), +3250° (280) (trough), +19500° (246) (peak), +14400° (238) (trough), +36700° (224). CD (c=0.0100, MeOH) [θ]^{23} (nm): +830 (300), +2640 (290), +160 (256), +10920 (237), +1010 (230), +17890 (220).

The amorphous **1** (8 mg) was crystallized as its hydrochloride, mp 223—224° (from EtOH) (lit.[4] mp 223—224°). *Anal.* Calcd for $C_{18}H_{21}NO_5\cdot HCl$: C, 58.77; H, 6.03; N, 3.81. Found: C, 58.49; H, 6.10; N, 3.30. Treatment of the hydrochloride of **1** with picric acid gave its picrate, mp 202—203° (dec.) [lit.[4] mp 204—205° (dec.)].

The base (**1**) thus obtained from **3** by MnO_2 oxidation was identical with an authentic sample of **1** from the natural source as judged by direct comparison of the spectral data for the free bases and salts and by the mixed melting point test.

Fraction II gave **2** (7 mg, 9.4%), mp 202—203°, which was identical with an authentic sample of **2** by direct comparison. ORD (c=0.0109, MeOH) [M]^{20} (nm): +1820° (350), +2430°(310) (peak), +1820° (298) (trough), +24800° (248) (peak), +3640° (229) (trough), +15800° (222). CD (c=0.0987, MeOH) [θ]^{23} (nm): −1680 (300), −3700 (298), +32270 (239), +18120 (223), +28840 (218).

Fraction III gave **13** (16 mg, 21.6%), mp 125—127° (from acetone) (lit.[5c] mp 130—131°). $[\alpha]_D^{17}$ +267.0° (c=0.54, $CHCl_3$) [lit.[5c] $[\alpha]_D^{24}$ +276° (c=0.95, $CHCl_3$)]. *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.58; H, 5.57; N, 4.19. IR ν_{max}^{KBr} cm^{-1}: 1730, 1710 (CO), 1610 (C=C).

Oxidation of Tazattadiol (6) with MnO_2——A mixture of **6** (100 mg) in $CHCl_3$ (10 ml) and MnO_2[12] (500 mg)

12) J. Attenburrow, A.F.B. Cameron, J.H. Chapman, R.M. Evans, B.A. Hems, A.B.A. Jansen, and T. Walker, *J. Chem. Soc.*, **1952**, 1094.

was stirred at room temperature for 1 hr. Work-up in the usual way gave an oil (105 mg), which, when subjected to PLC using Al_2O_3–[benzene-acetone (4: 1)], gave three fractions: I, *Rf* 0.08—0.22; II, *Rf* 0.33—0.52; III, *Rf* 0.66—0.82. Each fraction was eluted with $CHCl_3$–MeOH–acetone (1: 1: 1). Fraction I gave **6** (12 mg), mp 112—117°. Fraction II gave amorphous **14** (35 mg, 35.2%). $[\alpha]_D^{19}$ +195.0° (*c*=0.48, MeOH) [lit.[5b] $[\alpha]_D^{24}$ +188° (MeOH)]. MS *m/e*: Calcd for $C_{18}H_{21}NO_5$: 331.1418. Found: 331.1378. ORD (*c*=0.0108, MeOH) $[M]^{26}$ (nm): +3060° (350), +4570° (302), +27500° (253) (peak), +12800° (236) (trough), +27500° (226). CD (*c*=0.0100, MeOH) $[\theta]^{23}$ (nm): −660 (300), −1820 (286), 0 (266), +24920 (239), +17560 (227), +31450 (220).

Fraction III gave **15** (20 mg, 20.4%), mp 105—108° (from ether). $[\alpha]_D^{17}$ +142.0° (*c*=0.52, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.76; H, 5.88; N, 4.06. IR ν_{max}^{KBr} cm^{-1}: 1720 (CO), 1620 (C=C).

Deoxytazettine (**7**)[9]——ORD (*c*=0.0101, MeOH) $[M]^{20}$ (nm): +3120° (350), +4980° (295), +25600° (251)(peak), +12500° (234) (through), +26800° (224). CD (*c*=0.0096, MeOH) $[\theta]^{23}$ (nm): −6530 (300), −9830 (287), 0 (267), +21250 (241), +11450 (226), +30000 (218).

Deoxytazettine Neomethine (**8**)[9]——(i) The sample from the natural source: ORD (*c*=0.0049, MeOH) $[M]^{27}$ (nm): −1220° (350), −8520° (304) (trough), −7070° (290) (peak), −13570° (278) (trough), 0° (268), +21920° (253) (peak), +610° (242). CD (*c*=0.0081, MeOH) $[\theta]^{23}$ (nm): −4250 (300), −18630 (264), −5960 (246), −33090 (232), 0 (221), +33940 (215).

(ii) The synthetic sample: ORD (*c*=0.0030, MeOH) $[M]^{27}$ (nm): −1980° (350), −11970° (304) (trough), −9980° (292) (peak), −16960° (278) (trough), 0° (268), +21950° (252) (peak), +780° (242). CD (*c*=0.0103, MeOH) $[\theta]^{23}$ (nm): −4320 (300), −20860 (264), −8650 (246), −33000 (232), 0 (222), +28810 (215).

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